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History and Evolution of the Dissolution Test

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INTRODUCTION

The release of the drug substance from a solid dosage form has a major impact on its rate and extent of absorption. In certain instances, as is the case with modified-release formulations, the rate-limiting step in the appearance of the drug in the systemic circulation is its release from the formulation.

In the vast majority of cases, in vitro dissolution of an immediate-release product is one of the most important tools in assuring the batch-to-batch quality of the drug product. Establishing appropriate dissolution specifications will assure that the manufacture of the dosage form is consistent and successful throughout the product's life cycle and that each dosage unit within a batch will have the same pharmaceutical qualities that correspond to those shown to have an adequate safety and efficacy profile. Due to the critical role that dissolution plays in the bioavailability of the drug, in vitro dissolution can serve as a relevant predictor of the in vivo performance of the drug product.

This article discusses the history as well as the evolution of dissolution and its role in the drug development and approval process

EVOLUTION OF DRUG DISSOLUTION TESTING

The first dissolution studies were reported in the literature in 1897 by Noyes and Whitney (*1*) where they studied the dissolution of two sparingly soluble compounds, namely benzoic acid and lead chloride. The chemical substances were laid around glass cylinders that were submerged into vessels containing water. These cylinders were rotated at constant speed and were held under constant temperature. Their fundamental work led to the well-known equation in physical pharmacy, the Noyes–Whitney equation. Even though there was a lot of activity investigating dissolution from the physical–chemical point of view, it was not until the early 1950s that pharmaceutical scientists started to realize the importance of dissolution on the rate of absorption of orally administered drugs. Edwards (*2*) in 1951 postulated that the rate-limiting step in the absorption of aspirin in the bloodstream was its dissolution. In 1957 Nelson (*3*) was the first scientist to explicitly relate the blood levels of orally administered theophylline to its dissolution.

However, in the mid 1960s realization of the impact of dissolution on the therapeutic effect of orally administered drugs began. Reports published in the early 1960s drew attention to the lack of efficacy of two brands of tolbutamide marketed in Canada (*4*). Tablets with much slower disintegration and release characteristics showed a marked decrease in plasma levels. Such observations were confirmed with other products such as chloramphenicol and diphenylhydantoin (*5*). In 1971 Lindenbaum (*6*) observed a seven-fold difference in digoxin serum levels among the different digoxin formulations. This finding prompted FDA to investigate the dissolution of 44 lots of digoxin from 32 different manufacturers. The study revealed a wide difference in in vitro release characteristics of the different lots, thus explaining the observed bioinequivalence (*7*). In the case of phenytoin, increased toxicities were observed when the manufacturer replaced calcium sulfate with lactose (*8*). This resulted in higher concentrations due to faster dissolution rate attributed to the more hydrophilic nature of lactose compared with calcium sulfate.

The net outcome of all the above cases was the introduction of dissolution requirements by both the FDA and USP. As a result, the dissolution test became a quality control tool to ensure lot-to-lot consistency. In 1971 the basket-stirred flask test (USP Apparatus 1) was adopted as an official dissolution test in six monographs. In 1978 the paddle method (USP Apparatus 2) was introduced, and a general chapter on drug release was published in *USP 21* in 1985. In 1991 the reciprocating cylinder (USP Apparatus 3) for modified-release formulations and in 1995 the flow-through cell (USP Apparatus 4) for extended-release formulations were adopted. Currently there are seven official apparatus described in the USP (*9*).

The year 1997 was a turning point for dissolution as FDA released four guidances that pertain to in vitro dissolution and its application from a regulatory point of view. The first guidance (*10*) outlines the general expectations of FDA regarding dissolution of IR dosage forms as well as the statistical methods used to compare the similarity/dissimilarity between two dissolution profiles. The FDA adopted the f_2 test proposed by Moore and Flanner (*11*) to declare similarity of two dissolution profiles. The f_2 equation shown below should be used only when the variability is not greater than 20% and dissolution is not fast (if greater than 85% is achieved in 15 min, then there is no need to compare the two profiles as they are considered fast and exhibit no difference).

$$f_2 = 50 \cdot \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

An f_2 value greater than 50 indicates that the two profiles are similar, and an f_2 value less than 50 indicates that the release characteristics are different. In the case where the f_2 test cannot be used due to excessive variability, the FDA guidance suggests other parametric tests that could be used to determine the difference between two profiles such as the mean standard difference and the f_2 bootstrap method.

At the same time in September 1997, the FDA released a guidance on in vitro in vivo correlations for modified-release formulations (*12*) that outlined the general expectations on the development, evaluation, and applications of IVIVC. In this guidance, three levels of correlations were defined. This guidance also defined the criteria for the acceptance and rejection of an IVIVC based on both the internal and external ability to predict C_{max} and *AUC*. Moreover, this guidance had specific recommendations on how to set the dissolution specifications for modified-release in both the presence and absence of an IVIVC. This guidance really shifted the way dissolution specifications were set because it specifically stipulated that variability in release characteristics should no longer be considered when setting the dissolution specification. The IVIVC guidance was also a milestone since for the first time it allowed the approval of manufacturing changes with only comparative dissolution data based on in vivo predictions that usually would have required in vivo studies for approval.

At the same time, FDA released two guidances on scale-up and post-approval changes for both IR (*13*) and MR products (*14*). These guidances outline the type of data needed to approve manufacturing changes. Both Level 1 and Level 2 changes for most part could be approved on comparability of the dissolution profiles in multimedia.

The release of these guidances demonstrated the heavy reliance of FDA on in vitro dissolution to rule out bioinequivalence and confirmed the use of in vitro dissolution as a surrogate for in vivo bioequivalence. The regulatory basis for granting a waiver of the requirement for the submission of in vivo bioavailability/bioequivalence (BA/BE) data is derived from the Code of Federal Regulations (*15*). This states that either an in vitro test that has been correlated with and is predictive of human bioavailability or a currently available in vitro test that ensures adequate human in vivo bioavailability is acceptable for the evaluation of BA/BE. Based on this section of the CFR, a variety of biowaivers can be granted. The CFR states specifically that a biowaiver can be obtained for lower strengths of the same dosage form or for a reformulated product that is identical except for a different color, flavor, or preservative that is not likely to affect the bioavailability.

BCS Classification

To further illustrate the use of in vitro dissolution as a surrogate for in vivo bioavailability, in 2000 the FDA released a guidance on obtaining in vivo bioavailability waivers based on the Biopharmaceutics Classification System (*16*). The scientific basis of this guidance is the work published by Amidon et al. (*17*). The guidance classifies drug substances into four categories as shown in Table 1. A highly soluble drug substance is defined as one where the highest dose strength dissolves in 250 mL or less of aqueous media over the pH range of 1–7.5. A highly permeable drug is defined as a drug whose absolute bioavailability is greater than 90% as determined by in vitro permeation studies. An in vivo bioavailability/bioequivalence waiver could be granted for a fast-dissolving BCS Class 1 drug. A fast-dissolving drug product is defined as a drug product that has greater than 85% dissolved in 15 min over the pH range of 1–7.5. A new or generic oral immediate-release drug product could be approved based on in vitro dissolution data alone without having to conduct in vivo studies. It should be noted that the designation of BCS Class 1 is imparted by a special committee within the FDA composed of the clinical pharmacology, biopharmaceutics, and office of generic drug scientists. However, it is important to remember that this guidance only applies to immediate-release formulations and does not apply to any other routes or modified-release formulations. The release of this guidance as well as the IVIVC guidance demonstrates the heavy reliance of FDA on dissolution as a predictor of in vivo bioavailability differences and its use as a tool to alleviate the regulatory burden by decreasing the number of in vivo studies required to approve and maintain a drug product on the market. However, for dissolution to be a useful, accurate, and precise tool, certain factors must be considered, as outlined below.

CONSIDERATIONS FOR THE DEVELOPMENT OF AN OPTIMAL DISSOLUTION METHOD

According to the FDA guidance (*10*), the dissolution characteristics of the drug product should be developed considering the pH solubility profile and pK_a of the drug substance. The drug permeability or octanol/water partition coefficient measurement may be also useful in selecting the dissolution methodology and specifications. For NDAs, the specifications should be based on the dissolution characteristics of batches used in pivotal clinical trials, confirmatory bioavailability studies, or both. If the formulation intended for marketing differs significantly from the drug product used in pivotal clinical trials, dissolution and bioequivalence testing between the two formulations are recommended.

Dissolution testing should be carried out under mild test conditions, using the basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15-min intervals, to generate a dissolution profile. For rapidly dissolving products,

Table 1. Biopharmaceutics Classification System

	High Permeability	Low Permeability
High Solubility	Class 1	Class 3
Low Solubility	Class 2	Class 4

generation of an adequate profile sampling at 5- or 10-min intervals may be necessary. For highly soluble and rapidly dissolving drug products (BCS Classes 1 and 3), a single-point dissolution test specification of NLT 85% ($Q = 80\%$) in 30 min or less is sufficient as a routine quality control test for batch-to-batch uniformity. For slowly dissolving or poorly water soluble drugs (BCS Class 2), a two-point dissolution specification, one at 15 min to include a dissolution range (a dissolution window) and the other at a later point (30, 45, or 60 min) to ensure 85% dissolution, is recommended to characterize the quality of the product. The product is expected to comply with dissolution specifications throughout its shelf life. If the dissolution characteristics of the drug product change with time, whether or not the specifications should be altered will depend on demonstrating bioequivalence of the changed product to the original bio-batch or pivotal batch. To ensure continuous batch-to-batch equivalence of the product after scale-up and post-approval changes in the marketplace, dissolution profiles should remain comparable to those of the approved bio-batch or pivotal clinical trial batch(es).

In many instances for poorly soluble drugs (BCS Class 2 or 4), to obtain complete and fast dissolution of the drug product, increased amounts of surfactant, organic, or hydro-alcoholic solutions are used as the dissolution medium in combination with relatively vigorous agitation speeds resulting in fast dissolution. Although it is possible to obtain complete dissolution of the drug from the formulation, such dissolution tests provide little value as a quality control tool because of poor discriminating ability. For such dissolution methods and conditions to be acceptable and useful from a regulatory point of view, one should demonstrate the discriminating ability of the method. This can be accomplished by showing that the method can differentiate between formulations with widely different in vivo release characteristics or alternatively, by showing that the method can reject lots that are not acceptable from a chemistry and manufacturing point of view. This is commonly done with drug-eluting stents where the sponsors generate data to show that the dissolution method is able to reject stents with unacceptable release characteristics by intentional manipulation of the formulations. For such a drug–device combination where the intended use is over a relatively long period of time (months to years) and where the therapeutic effect cannot be easily reversed, it is crucial that the dissolution method provides the necessary quality assurance. Moreover, it becomes an extremely important tool in assessing certain chemistry and manufacturing changes since conducting in vivo bioequivalence studies in human volunteers is practically impossible.

Minimizing Variability to Obtain Consistent In Vitro Release Characteristics and Optimal Therapeutic Benefit

In the past, it was usual and customary to set dissolution specifications based on the variability in the in vitro dissolution data. The end result of this practice was the possibility of introducing lots on the market that were highly variable resulting in potentially wide fluctuations in plasma levels leading to a variable therapeutic effect and increased incidence of adverse events. Moreover, this practice of setting the limits to ±3 standard deviations tended to reward manufacturers with poor and highly variables formulations. Therefore, manufacturers with poor manufacturing and process controls would have products with relatively wider dissolution specifications compared with manufacturers with very tight controls. Thus, the FDA is no longer accepting such a practice and now stipulates that variability should no longer be a consideration in setting dissolution specifications. This change in policy would force drug manufacturers to tighten their manufacturing controls and to develop less variable dissolution methods.

Individual versus Mean Performance

It has been a common practice of manufacturers to propose dissolution specifications based on passing the specifications at Stage 1 of the USP acceptance criteria (all the individual units meet the specifications). This practice would result in some units (outliers) driving the specifications. If the premise that all units should meet the acceptance criteria were accepted, this would result in dissolution specifications that would allow the release of lots with markedly different release characteristics. Such specifications would not ensure consistency from lot to lot and would not provide the best product to the patient. It is a misconception to believe that if a lot fails to meet the dissolution specification at Stage I of USP testing, the manufacturing process is not well controlled. In fact, from a regulatory point of view, a failure exists when the lot fails to meet the acceptance criteria at Stage 3 of testing. In view of the above consideration, setting the dissolution specifications based on average performance (ability to pass Stage 2 testing) results in acceptance criteria that would minimize the probability of the release of lots with atypical performance and therefore ensure a more consistent therapeutic effect to the patient.

Assurance of Complete Dissolution of the Drug Product

The specification for amount of drug dissolved is another important consideration in ensuring that the patient always gets the same therapeutic dose from lot to lot. For drugs that exhibit complete dissolution, setting the highest Q value possible would minimize the variability in the dose delivered to the subject. In an ideal situation, one would like to see a Q value of 100%; from a practical point of view, this is not possible due to the fact that there is inherent variability both in the content uniformity of the dosage form and in the dissolution test. For monographs of older drugs, a Q value of greater than 75% is seldom observed for completely dissolving drugs. However, in recent years, it is more common to see the Q value set at 80% with some cases at 85%. Such a specification would not allow the release of lots that on average differ by more

than 20% in amount of drug delivered and thus minimize the probability of bioinequivalence.

Appropriate Dissolution Time Specifications

While the choice of time points for modified-release formulations is clearly defined in the 1997 guidance on in vitro–in vivo correlations for extended-release oral dosage forms (*12*), there is a debate on establishing the optimal dissolution time point for IR formulations. Most sponsors prefer setting dissolution specifications at times faster than 30 min even though their product might be completely dissolved in 5 or 10 min. It is believed that setting a faster dissolution time specification would not translate into in vivo bioavailability differences, and therefore dissolution time points faster than 30 min will produce an undue manufacturing burden without achieving any benefit. At present, it is not uncommon that both sponsors and regulators consider dissolution time point specifications as early as 15 min for fast dissolving formulations (100% in less than 10 min). Such early time points will minimize the introduction of lots with markedly different dissolution characteristics and will ensure a more consistent performance from lot to lot.

ROLE OF DISSOLUTION IN IMPLEMENTING QUALITY BY DESIGN (QBD) AND IN DEFINING THE DESIGN SPACE

Dissolution testing is a potentially powerful Critical Quality Attribute (CQA) for the development of a drug product given that it is influenced by many different material and process inputs (e.g., raw material particle size, compression pressure, moisture) and that it can be a predictor of in vivo drug performance. Therefore, it is commonly used as one of the endpoints in defining the design space for a given drug product. Design space in this context is defined as the multidimensional combination and interaction of input variables (material attributes) and process parameters that have been demonstrated to provide assurance of quality.

Dissolution testing plays an important role in the QbD approach. Under the QbD paradigm, dissolution testing can be used to establish a relationship between (CQA) and in vitro test methods. Thus, in a QbD approach, a design specification including intended use of the procedure and performance objectives (e.g., less than 20% released at 30 min, greater that 80% at 10 h, 12-h duration) is agreed upon a priori. A structured approach such as statistical design of experiments is used to identify the relationship between in vivo release profiles and method conditions (medium, apparatus, sampling procedure, etc.) and the response surface (in vitro release profiles). This information is used to identify critical method parameters for controlling the release profile and the ability of the method to predict drug bioavailability. A similar procedure can be used in formulation development to identify CPIs that influence the release profile of the product and that can be controlled to ensure final drug product quality. If a relationship between these components is established, it may be possible to waive dissolution testing in product release if other tests prove that the product specifications have been met (i.e., disintegration testing) and if the parameters in the design space are closely defined and monitored.

Three possible scenarios that describe the role of dissolution in setting a clinically meaningful design space are discussed below.

Case I: No Data Relating In Vitro Dissolution with In Vivo Bioavailability

In such a case, dissolution can be still used as an endpoint to define the design space. However, the dissolution method should be sensitive and discriminating to pick up difference in the critical manufacturing variable. In addition, the dissolution endpoint selected should be based on the performance of the clinical and bio lots that were shown to be safe and effective. The above-described scenario is illustrated in Figure 1 and can be summarized as follows:

1) Produce dosage forms variants with different in vitro release characteristics.
2) Select the optimal dissolution method that provides an adequate discriminating power.
3) Design space should be chosen to ensure similar vitro release characteristics (by f_2 testing or other appropriate means).

The optimal design space should contain all lots with release characteristics similar to the lots that were shown to be safe and effective. Even though the regulatory decision is made solely on in vitro considerations, the quality risk is minimized and the clinical benefit is optimized given that no lots with different release characteristics would be approved for release on the market.

Case II: Established In Vitro Release Characteristics Resulting in Bioequivalence

In this scenario, even though a formal predictive in vivo in–vitro correlation is not established, the range of

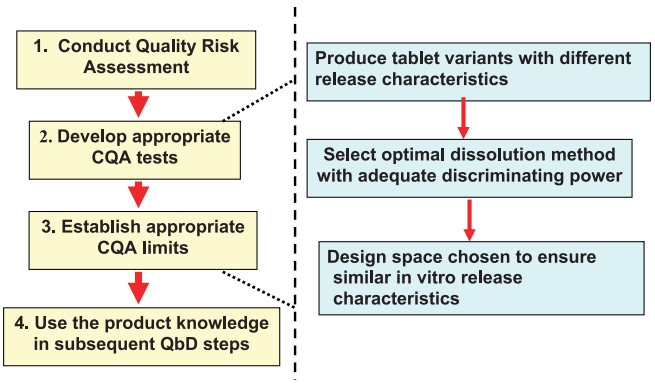

Figure 1. Role of dissolution in defining the design. Case I: no data relating in vitro dissolution with in vivo bioavailability.

dissolution profiles or release characteristics resulting in bioequivalence is already defined. This scenario is illustrated in Figure 2 where the different dosage form variants are tested in vivo to determine their in vivo bioavailability. The dissolution profiles resulting in bioequivalence are defined, enabling the determination of acceptable boundaries resulting in similar in vivo performance. In this case, the design space is chosen to result in bioequivalent performance within the design space.

Case III: Presence of In Vivo–In Vitro Correlation (IVIVC)

This is the most desirable scenario and most applicable to modified-release formulations (Figure 3). In such a case, the rate-limiting step in the appearance of the drug in the systemic circulation is its release from the dosage form. In the presence of an acceptable IVIVC model, the dissolution method is considered biorelevant allowing for the establishment of clinically relevant dissolution specifications. An acceptable IVIVC model allows for the estimation of the dissolution profile from the drug product that would be bioequivalent to the reference (a target profile for this product). The dissolution profiles predicted by the IVIVC model can then be used in setting acceptable design space boundaries that are clinically meaningful (*18*, *19*).

The general steps in setting the design space in the presence of a validated IVIVC are as follows:

1) Produce dosage forms variants with different in vitro release characteristics.
2) Select the optimal dissolution method that provides an adequate discriminating power and is predictive of the in vivo performance.
3) Determine the bioavailability for all the dosage form variants.
4) Establish correlation between the in vitro dissolution and in vivo bioavailability (preferably a level A correlation).
5) Choose a design space based on predicted plasma concentrations that are bioequivalent to the target (clinical) formulation.

In all the above scenarios with varying levels of assurance, dissolution is used as a valuable tool to define the design space that will ensure consistent in vivo performance similar to that of the clinical trial lots.

In both Case II and III, one is able to make informed decisions on critical manufacturing variables taking into account the impact on in vivo performance. Therefore, any chosen control steps or specifications are tied to the clinical outcome. This is somewhat a shift in paradigm because in the past, any regulatory decision concerning chemistry and manufacturing was based solely on manufacturing capabilities and in vitro considerations. At present, dissolution is proving to be not only a valuable tool that enables an optimal quality control of the product but also a link of manufacturing considerations to clinical outcomes optimizing the therapeutic benefit.

CONCLUSION

The dissolution test has evolved into a reliable surrogate for bioavailability. It is extensively used by FDA and the pharmaceutical industry in the various stages of drug development (see Figure 4) from checking the integrity of the dosage form (such as the alcohol dose-dumping studies for modified-release formulations), to bridging between the clinical and market formulation (*20*), to predicting the plasma concentration–time profile in the presence of IVIVCs. Due to this increase reliance on dissolution testing, FDA formed a separate group within the Office of New Drug Quality Assessment to evaluate the biopharmaceutics aspects of a drug product. Part of its responsibilities is to assure that the dissolution method and specifications are chosen and set appropriately. Since many regulatory decisions hinge on the dissolution method, FDA is encouraging firms to submit the dissolution method development report as early as possible during the IND phase of drug development and to assure the adequacy of the proposed method. Therefore, adequate effort and resources should be devoted to develop the most sensitive and discriminating method that will be able to

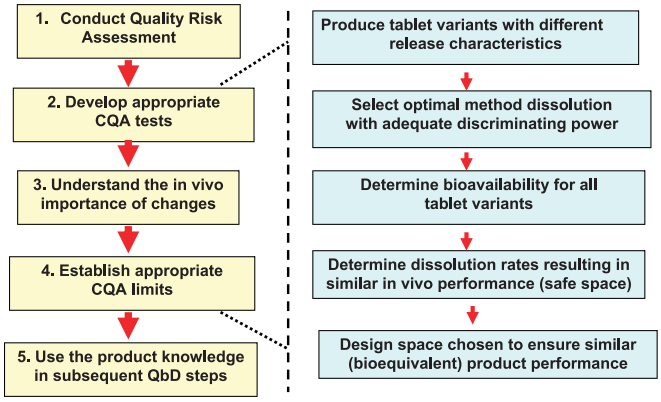

Figure 2. Role of dissolution in defining the design. Case II: established in vitro release characteristics resulting in bioequivalence.

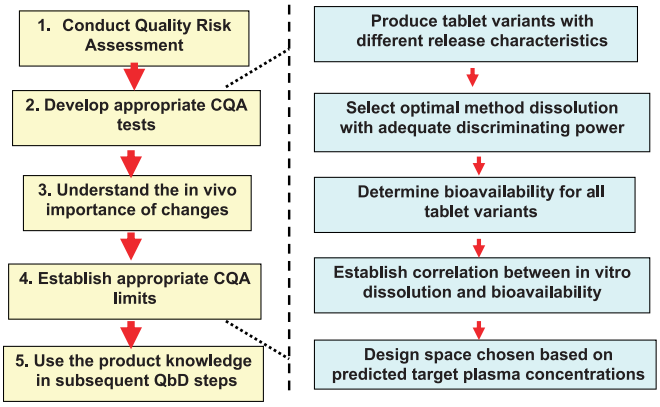

Figure 3. Role of dissolution in defining the design. Case III: presence of in vivo–in vitro correlation (IVIVC).

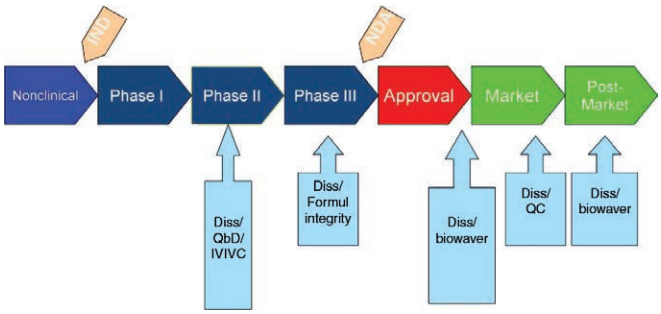

Figure 4. Role of dissolution in the various stages of drug development.

pick up meaningful differences in release characteristics and therefore minimize the probability of the introduction of lots with inadequate in vivo performance.

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